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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/671,461	09/27/2000	Arne Staby	5784.210-US	6001

23650 7590 01/11/2006

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 01/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/671,461	STABY, ARNE	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4,6 and 11-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4,6 and 11-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 September 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/522,694.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/31/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 2, 4, 6 and 11-29 are pending.

Applicants' amendment filed on October 31, 2005 is acknowledged. Applicants' response has been fully considered. Claim 4 has been amended, and new claims 26-29 have been added. Thus, claims 2, 4, 6 and 11-29 are examined.

Withdrawn Claim Rejections-Obviousness Type Double Patenting

2. The previous rejection of claims 2, 4, 6 and 11-25 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3, 4, 8, 9 and 12-38 of co-pending application 10/176,410 (based on the amendment filed March 17, 2005), is withdrawn in view of applicants' response at pages 7-8 of the amendment filed October 31, 2005.

Informalities

3. The disclosure is objected to because of the following informalities:

The specification recites the term "$Arg^{34}GLP\text{-}1_{(7\text{-}37)}$" at page 6, line 18, however, it also recites the terms such as "$Val^{8}GLP$-1(7-37)" and "$Thr^{8}GLP$-1(7-37)" at page 6, line 16. For consistency, use of "$Arg^{34}GLP$-1(7-37)" is suggested.

Drawings

4. The drawings are objected to, please see attached notice of draftsperson's drawing review.

Claim Objection

5. Claims 15 and 23 are objected to because of the use of the term "$Arg^{34}GLP\text{-}1_{(7\text{-}37)}$". For consistency, use of "$Arg^{34}GLP$-1(7-37)" is suggested.

New Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 2, 4, 6 and 11-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method or an industrial method for purifying a peptide or a specific peptide cited in claim 21 from a mixture comprising said peptide and related impurities, said method comprising: a) eluting said related impurities of said mixture from an anion exchange chromatography matrix using a solution comprising an organic modifier, water, and a buffer, and optionally a salt component at a linear or step gradient or isocratically in salt component, and at pH-values maintained with a buffer so that said peptide has a negative local or overall net charge and said related impurities have a local or overall negative net charge which is lower than the negative net charge of said peptide so as to remove said related impurities; and b) subsequently, eluting said peptide in the absence of an organic modifier, by a step or linear change to an aqueous solvent optionally with a salt component, at the same or lower pH-values maintained with a buffer, does not reasonably provide enablement for a method or an industrial method for purifying a peptide or a specific peptide cited in claim 21 from a mixture comprising said peptide and related impurities, said method comprising: a) eluting said related impurities of said mixture from an anion exchange chromatography matrix using a solution comprising an organic modifier, water and optionally a salt component, but without a buffer in step (a), and b) subsequently, eluting said peptide in the absence of an organic modifier, by a step or linear change to an aqueous solvent optionally with a salt component, at the same or lower

pH-values maintained without a buffer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 2, 4, 6 and 11-29 encompass a method or an industrial method for purifying a peptide or a specific peptide for purifying a peptide from a mixture comprising said peptide and related impurities, by eluting said related impurities of said mixture from an anion exchange chromatography matrix using a solution comprising an organic modifier, water, optionally a salt component and optionally a buffer; and subsequently, eluting said peptide in the absence of an organic modifier, by a step or linear change to an aqueous solvent optionally with a salt component, at the same or lower pH-values optionally maintained with a buffer. The specification, however, only discloses cursory conclusions without data supporting the findings, which state that the present invention relates to an anion exchange chromatography process for purifying a peptide from a mixture comprising said peptide and related impurities using a solution comprising an organic modifier, water, optionally a salt component and optionally a buffer in step (a), and a solution without an organic modifier in step (b) (page 3). There are no indicia that the present application enables the full scope of the claims in view of a method of purifying a peptide from a mixture comprising said peptide and related impurities using an anion exchange chromatography as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to how the full scope of the claims is encompassed. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the presence or absence of working

examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses a solution comprising an organic modifier, water, optionally a salt component, but without a buffer in step (a), and a solution without an organic modifier and at the same or lower pH values not maintained with a buffer in step (b) of the claimed methods, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

The specification demonstrates the purification of human insulin from mixtures by anion exchange chromatography using a solution containing ethanol as organic modifier, triethanolamine (pKa of 7.8) as a buffer for pH 7.5, and sodium citrate as a salt for step or linear gradient in step (a), and a solution containing a buffer (triethanolamine or citric acid) and a salt, but without ethanol (Examples 13-17). However, the specification has not demonstrated the use of a solution without a buffer to elute the impurities in step (a) or to elute the peptide in step (b) in the claimed method.

(3). The state of the prior art and relative skill of those in the art:

The prior art (e.g., Johnson *et al.*, Ion Exchange in "Basic Liquid Chromatography, pages 116-148 (1978)) teach the principles and conditions for performing ion-exchange chromatography, and the buffer is required to maintain a proper pH for ionization of ion exchange resins, and the specification also indicates the pH of solution is maintained so that the

peptide has a negative local or overall net charge and the related impurities have a local or overall negative net charge which is lower than the negative net charge of said peptide so as to remove said related impurities in step (a) (page 3). However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide teachings on how the pH of solution is stably maintained without a buffer, and how the local or overall negative net charge of related impurities is maintained to be lower than the negative net charge of said peptide, if the pH of the solution is not stable.

(4). Predictability or unpredictability of the art:

The claims encompass a method or an industrial method for purifying a peptide from a mixture comprising said peptide and related impurities, by eluting said related impurities of said mixture from an anion exchange chromatography matrix using a solution comprising an organic modifier, water, optionally a salt component and optionally a buffer; and subsequently, eluting said peptide in the absence of an organic modifier, by a step or linear change to an aqueous solvent optionally with a salt component, at the same or lower pH-values optionally maintained with a buffer. However, the specification does not describe how the pH of solution containing only water and organic modifier but without a buffer is stably maintained, the invention is highly unpredictable regarding the pH of the solution and the local or overall negative net charge of the peptide or impurities when the solution does not contain a buffer.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method for purifying a peptide from a mixture comprising said peptide and related impurities, by eluting said related impurities of said mixture from an

anion exchange chromatography matrix using a solution comprising an organic modifier, water, optionally a salt component and optionally a buffer. The specification demonstrates the purification of human insulin from mixtures by anion exchange chromatography using a solution containing ethanol as organic modifier, triethanolamine (pKa of 7.8) as a buffer for pH 7.5, and sodium citrate as a salt for step or linear gradient in step (a), and a solution containing a buffer (triethanolamine or citric acid) and a salt, but without ethanol (Examples 13-17). However, the specification has not demonstrated the use of a solution without a buffer to elute the impurities in step (a) or to elute the peptide in step (b) in the claimed method, nor has described how the pH of solution is stably maintained without a buffer, and how the local or overall negative net charge of related impurities is maintained to be lower than the negative net charge of said peptide, if the pH of the solution is not stable. Since the specification does not provide sufficient teachings on the use of a solution comprising an organic modifier, water, optionally a salt component, but without a buffer in the claimed method, it is necessary to carry out undue experimentation to check the pH of the solution without buffer, and to elute the impurities from the anion exchange chromatography the claimed method.

(6). Nature of the Invention

The scope of the claims encompasses a method for purifying a peptide from a mixture comprising said peptide and related impurities, by eluting said related impurities of said mixture from an anion exchange chromatography matrix using a solution comprising an organic modifier, water, optionally a salt component and optionally a buffer, but the specification does not provide sufficient teachings on the use of a solution comprising an organic modifier, water,

optionally a salt component, but without a buffer in the claimed method. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working examples do not demonstrate the claimed methods associated with variants, the teaching in the specification is limited, and the pH of the solution without a buffer is not predictable, and therefore, it is necessary to carry out undue experimentation to use the solution containing an organic modifier, water, optionally a salt component, but without a buffer in the claimed method.

Maintained Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Previous rejection of claims 2, 4, 6 and 11-25 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained, and new claims 26-29 have been added. Response to applicant's argument is shown below.

Claims 2, 4, 6 and 11-29 are indefinite because the claim recites the term "optionally a salt component and optionally a buffer", but it also indicates a solution comprising an organic modifier and water at a linear or step gradient or isocratically in salt component (this is not optional, which requires the presence of salt), and at pH-values optionally maintained with a buffer, thus it is not clear how a solution comprising an organic modifier and water, but without the presence of a salt component (optional) and a buffer (optional), can have a linear or step gradient or isocratically in salt component during the elution, and how the pH of the solution is maintained without a buffer (See Johnson et al., Ion Exchange in "Basic Liquid

Chromatography, pages 116-148 (1978) in Art of Record). Claims 6, 11-20 and 22-29 are included in the rejection because they are dependent on rejected claims and do not correct the deficiency of the claim from which they depend.

Response to Arguments

Applicants indicate the phrase "a solution comprising an organic modifier, water, optionally a salt component and optionally a buffer" would be clearly understood to mean that the solution used in step (a) of the claimed methods can contain: 1) organic modifier and water; 2) organic modifier, water and buffer; 3) organic modifier, water and salt; or 4) organic modifier, water, buffer and salt. Further, the phrase "at a linear or step gradient or isocratically in salt component" would be understood to mean that if salt is present in the solution described above, then use of the salt-containing solution in a linear or step gradient would be carried out by using a linear or step gradient of the salt component of the solution (as indeed was done in Examples 13-17). Regarding how the pH of an eluted solution can be maintained in the absence of buffer, applicants provide an example to illustrate the pH of the solution A can be adjusted to make a gradient (pages 8-9 of the response).

Applicants' response has been fully considered, however, the argument is not found persuasive because the claim recites the method using the solution comprising an organic modifier and water, at a linear or step gradient or isocratically in salt component, which requires the presence of the salt component in the solution, however, the recitation of "optionally a salt component and optionally a buffer" indicates the solution can be carried out without salt or buffer, which is not consistent with the former condition. Applicants argue that "if" salt is present in the solution, then this linear or step gradient or isocratic condition can be carried out,

which is not the case in the claimed method, the claimed method requires the salt component in the solution to carry out a linear or step gradient or isocratically in salt component during the elution, which is not indicated as being optional. Regarding the pH of the solution can be maintained without a buffer during the elution, the argument is also not persuasive because even the pH of the solution can be adjusted to a certain pH, since there is no buffer, it is not clear how the pH of the solution can be properly maintained (See Johnson et al. (1978) especially pages 135-137). The recitation of Examples 13-17 by the examiner in the previous rejection merely indicates the solution used in step (a) of the claimed method contains ethanol as organic modifier, triethanolamine (pKa of 7.8) as a buffer for pH 7.5, and sodium citrate as a salt for step or linear gradient.

Perhaps claim 2 can be amended as follows:

A method for purifying a peptide from a mixture comprising said peptide and related impurities, said method comprising:

a) eluting said related impurities of said mixture from an anion exchange chromatography matrix using a solution comprising an organic modifier, water, ~~optionally a salt component~~ and ~~optionally~~ a buffer, and optionally a salt component at a linear or step gradient or isocratically in salt component, and at pH-values ~~optionally~~ maintained with a buffer so that said peptide has a negative local or overall net charge and said related impurities have a local or overall negative net charge which is lower than the negative net charge of said peptide so as to remove said related impurities; and without an intervening step,

b) subsequently, eluting said peptide in the absence of an organic modifier, by a step or linear change to an aqueous solvent optionally with a salt component, at the same or lower pH-

values ~~optionally~~ maintained with a buffer.

Conclusion

7. No claims are allowed.

Art of Record

Johnson *et al.* (Ion Exchange in "Basic Liquid Chromatography, pages 116-148 (1978)) teach the principles and conditions for performing ion-exchange chromatography, and the buffer is required to maintain a proper pH for ionization of ion exchange resins (page 137).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Patent Examiner

CHIH-MIN KAM
PATENT EXAMINER

CMK
December 30, 2005